REMARKS

This Preliminary Amendment constitutes the proper Submission with the RCE being concurrently filed and fully complies with M.P.E.P. § 706.07(h)(II).

Status of Claims

Upon entry of the present amendment, claims 1, 3-11, 13-15, 17-22 and 24 will remain pending in the above-identified application, with claims 1, 3-11, 13-15, 17 and 24 standing ready for further action on the merits, and remaining claims 18-22 being withdrawn from consideration based on an earlier restriction requirement of the Examiner. Claims 1, 9, 10, 13-15 and 24 have been amended herein.

The present amendments to the claims do not introduce new matter into the application as originally filed. For example, the amendments to claims 1, 15 and 24 have support in claims 9 and 24 as well as in the present specification at, e.g., page 10, line 19 and pages 22-23. With the changes to claim 1, claims 9, 10, 13 and 14 were appropriately amended.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. § 103(a)

As stated in the Final Office Action, claims 1, 3-11, 13-15, 17 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Public. No. 2004/0245662 to Chaubal et al. (hereinafter "**Chaubal '662**") in view of U.S. Patent No. 2,652,234 to Feldmann ("**Feldmann '234**"). Also, the Examiner has maintained this rejection as stated in the Advisory Action of August 7, 2009. Applicants respectfully traverse.

Applicants respectfully request reconsideration in light of the amendments to independent claims 1, 15 and 24 as shown herein. Applicants now recite the Microfluidizer or Nanomiser as the high-pressure homogenizer that is employed in the process of making ultrafine drug particles having an average particle size of 10 nm to 1000 nm. Also, the Microfluidizer or Nanomiser has a reservoir, a booster pump and an emulsifier, being connected via thin tubes, the injector being so configured as to feed a drug-containing solution containing a drug dissolved in a good solvent or a mixture of good solvents, the injector being integrated into the Microfluidizer or Nanomiser at any position of the channel for the circulating fluid in the thin tubes extending from the reservoir to the emulsifier. As the M.P.E.P. directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* M.P.E.P. § 2143.03. Reconsideration is respectfully requested in view of the claimed Microfluidizer or Nanomiser.

Applicants also note the advantages of the present invention. Specifically, by employing the Microfluidizer or Nanomiser, the present invention has unexpectedly achieved a method that produces ultrafine drug particles which are excellent in long-term dispersibility by preventing

precipitation and aggregation of drug particles. For instance, Applicants note Example 1 versus the Comparative Examples in Table 1 (page 28) of the specification[1]. Inventive Example 1 unexpectedly achieves better average particle size, especially when compared to the other examples not using a Microfluidizer. Applicants note that though Comparative Example 1 uses a Microfluidizer, the presently claimed method is not used (see also the discussion at pages 29-30 of the specification).

As stated on page 31 of the specification, these results clearly show that fine drug particles which are excellent in long-term dispersibility and have stable particle sizes substantially free from a significant increase can be obtained with the present invention. Also, the production method according to the present invention is an easy and convenient production method that can directly produce ultrafine drug particles at a set processing pressure using a Microfluidizer or Nanomiser without the need of a pretreatment step for adjusting the drug to have an average particle size of 100 μm or less. Such advantages are unexpected.

Regarding the current set of claims, Applicants also request reconsideration of the unexpected results of record. In particular, Applicants note that the claimed methods do not require a pretreatment step for adjusting the drug to have an average particle size at a predetermined level or less (generally 100 μm or less) in the production of ultrafine drug particles using the Microfluidizer or Nanomiser and can easily and conveniently carry out the treatment with the claimed methods. Additional surprising advantages of the present invention

[1] M.P.E.P. § 2145 clearly sets forth that rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36

include production of ultrafine drug particles even at a low energy output; and the ability to mix two solutions which are inherently difficult to mix with each other (see the present specification, at page 18, line 8 – page 21, line 21).

Regarding the comments in the Advisory Action that Applicants are not claiming the advantages or unexpected results of the present invention, Applicants note *In re Merchant*, 197 U.S.P.Q. 785, 788 (C.C.P.A. 1978), concerning objective evidence, as follows (*emphasis added*):

> Finally, the solicitor repeats the objection voiced by the examiner that the declaration is irrelevant because the claims specify neither the unexpected result nor the "features" that produce that result. *We are aware of no law requiring that unexpected results relied upon for patentability be recited in the claims*. The "features" referred to by the examiner are the conditions of pressure, feed rate, and reactor retention time for the commercial operation described in the declaration. We are equally unaware of any law requiring that commercial production parameters be claimed. Moreover, the "feature" responsible for appellant's unexpected results is recited in the claims, viz., "substantially anhydrous."

(Applicants' emphasis added.) Thus, Applicants do not have to claim, e.g., low energy output and the ability to mix two solutions in the claims.

Regarding the comments in the Advisory Action concerning whether the results are unexpected, once Applicants have presented rebuttal evidence, then USPTO office personnel should reconsider any initial obviousness determination in view of the entire record. Office personnel should not evaluate rebuttal evidence for its "knockdown" value against the *prima facie* case, *Piasecki,* 745 F.2d at 1473, 223 USPQ at 788, or summarily dismiss it as not compelling or insufficient. If the evidence is deemed insufficient to rebut the *prima facie* case of

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USPQ2d 1089, 1094-95 (Fed. Cir. 1995), or by way of an affidavit or declaration under 37 C.F.R. § 1.132, e.g.,

obviousness, USPTO office personnel should specifically set forth the facts and reasoning that justify this conclusion.

It is also believed that the combination of Chaubal '662 with Feldmann '234 is improper. M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (U.S. 2007).

But here, the cited references do not disclose the use of a Microfluidizer or a Nanomiser in a method as claimed, or the advantages attained therefrom. Further, the cited primary reference of Chaubal '662 does not disclose circulating the poor solvent into the Microfluidizer or Nanomiser and then adding the drug-containing solution to the circulating solution. In addition, Chaubal '662 fails to disclose or teach a Microfluidizer or Nanomiser with an online injector. The cited secondary reference of Feldmann '234 fails to account for the deficiencies of the primary reference. Thus, the

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Soni, 54 F.3d at 750, 34 USPQ2d at 1687.

Graham factors, including ascertaining the differences between the prior art and the claims that are at issue and evaluating evidence of secondary considerations, weigh in Applicants' favor.

Based on the above and the evidence or record, it is believed that this rejection has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: SEP 30 2009

Respectfully submitted,

By _____

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